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# Coloboma, Mental Retardation, Hypogonadism, and Obesity: Critical Review of the So-Called Biemond Syndrome Type 2, Updated Nosology, and Delineation of Three "New" Syndromes

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**Biemond syndrome type 2 (BS2) is classically regarded as a recessively inherited condition (MIM 210350) comprising mental retardation, coloboma, obesity, polydactyly, hypogonadism, hydrocephalus, and facial dysostosis. Clinically, the disorder is closely related to Bardet-Biedl syndrome. Few cases have been reported, most of them before 1970. We present clinical data on three mentally retarded sporadic cases with coloboma, obesity, and hypogenitalism (in two of them), fitting at first glance a diagnosis of BS2.**

**A review documents striking clinical variability among the patients said to have BS2. We propose a new nosology of those cases and delineate several new clinical forms. Purported BS2 cases may be divided into: (1) Bardet-Biedl syndrome with fortuitous coloboma or aniridia, (2) BS2 sensu stricto, a recessively inherited syndrome of sexual infantilism, short stature, coloboma, and preaxial polydactyly without obesity, only known from the original report, (3) a "new" dominantly inheri ted form of colobomatous microphthalmia occasionally associated with obesity, hypogonadism, and mental retardation, to which our observations belong, (4) cytogenetically proven Rubinstein-Taybi syndrome (one case), (5) an unclassifiable, early lethal familial syndrome resembling Buntinx-Majewski syndrome, and (6) a "new" coloboma-zygodactyly-clefting syndrome. The latter two syndromes may result from chromosomal anomaly. Am. J. Med. Genet. 69:370–379, 1997.** © 1997 Wiley-Liss, Inc.

**KEY WORDS: Bardet-Biedl syndrome; Biemond syndrome type 2; coloboma; hypogonadism; mental retardation; obesity; Rubinstein-Taybi syndrome**

## INTRODUCTION

Biemond syndrome type 2 (BS2 - MIM 210350) is classically quoted in the differential diagnosis of Bardet-Biedl syndrome as a combination of iris coloboma, mental retardation, obesity, hypogenitalism, and postaxial polydactyly. Hydrocephalus, hypospadias, and facial dysostosis also may be present. Inheritance is disputed (AR or AD). Few cases have been reported, most of them before 1970. We present clinical data on three sporadic cases fitting the diagnosis of BS2 in its "common" sense and critically review the older literature, suggesting an updated nosology and differential diagnosis with boundaries with Bardet-Biedl and other clinically related disorders (Table I).

## CLINICAL REPORTS

### Patient 1

This boy (GF 7059) was born by caesarean section at the term of an uneventful pregnancy. There was no prenatal exposure to known teratogens. Microphthalmia was noted at birth. Hydrocephalus secondary to a large interhemispheric arachnoidal cyst was treated surgically in infancy. When examined at age 7, he was 129 cm tall, weighed 54 kg, and had an OFC of 53 cm. He had truncal obesity (Fig. 1a), short, tapering fingers, micropenis (<2 cm, stretched), small (<1 cm), descended testes, high forehead with deep nasal bridge, flat, small nose with a wider tip, short, and flat phil-

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TABLE I. Synoptic View of the Syndromes Discussed in This Report

| Diagnosis | Inher. | Fundus | Iris | Short stature | Obesity | Hypogenitalism | Hypo-spadias | Pre axial polydactyly | Post axial poly-dactyly | Syn-dactyly | Brachy-dactyly | MR | Deaf-ness | Neurological anomaly | Dia-betes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bardet Biedl | AR | Tapeto-retinal dystrophy | N | Y | Y | Y (primary in men, minor and heterogeneous in women) | N | N | Y | Y | Y | Variable | N | N | Y | Usually blind in adulthood<br>Frequent urogenital malformations<br>Proven genetic heterogeneity |
| Laurence-Moon | AR | RP | N | N | N | N? (cryptor-chidism) | N | N | N | N | N | Mild | N | Spastic paraplegia | N | ¼ had obesity |
| Prader-Willi | 15q11 anomaly | Hypopg-mented | N | Y | Y | Y | N | N | N | N | Y | Variable | N | Severe hypotonia in infancy | Y | Abnormal methylation pattern |
| Cohen | AR | Cone-rod dystrophy | N | Y | Y | N | N | N | N | N | N | Y | N | Hypotonia | N | Specific dysmorphism<br>Long, thin fingers<br>Leucopenia |
| Sussman | ? | N | N | Y | Y | Infantilism | - | N | Y (feet) | N | N | Y | N | Microcephaly, ptosis, ophthal-moplegia | N | Mitochondriopathy? |
| Alström-Hallgren | AR | Atypical RP | N | N | Y | N | N | N | N | N | N | N | Y | N | Y | Nephropathy<br>Cardiomyopathy |
| Edwards-Sethi | AR | RP | N | N | Y | Y | N | N | N | N | N | Y | Y | Minor pyramidal signs | Y | Allelic to previous? |
| Biemond type 2 | AR | N | Coloboma | Y | N | Y | N | Y | N | N | N | Y | N | N | N | |
| Coloboma-obesity-MR | AD | N or atypical RP | Coloboma, microphthalmia | N | Y | Variable | N | N | N | N | N | Y | N | N | N | Several cases in families with simple AD coloboma |
| Al Frayh-Hague | AR | N? | Coloboma, microphthalmia, anophthalmia | Y | N | Y | N | N | N | N | N | Y | N | N | N | |
| Blumel-Knicker | AR? | ? | Coloboma | N | N | - | Y | N | Y | N | N | Y | - | Hydro-cephalus, micro-polygyry, agenesis of CC | - | Heart and urinary defects<br>Early lethality<br>Isolated polydactyly in the family |
| Coloboma-zygodactyly-clefting | ? | N | Coloboma | Y | N | Cryptorchidism | Y | N | N | Y | N | Y | N | N | N | Labiopalatine cleft<br>Facial dysmorphism<br>Ear dysplasia |
| Rubinstein-Taybi | 16p13 deletion | N | Coloboma, glaucoma | Y | N | N | N | Some-times | N | N | N | Y | N | N | N | Large thumbs and toes<br>Facial dysmorphism |

trum, and downturned mouth (Fig. 1b). The upper lateral incisors and one of the lower lateral incisors were absent. On the left side, there was colobomatous microphthalmia and cataract. The right eye was microphthalmic, with microcornea, normal iris, coloboma of the retina, and ocular hypertension, but no evidence of retinal dystrophy (Fig. 1c). Formal IQ testing was not performed, but he was considered to function at a borderline level and was able to decipher letters. Results of metabolic screening and chromosome studies were normal.

***Family history.*** Our propositus is the only child of nonconsanguineous, healthy Italian parents, ages 25 and 23, respectively, at time of birth. Fundi were normal in both.

### Patient 2

This boy was a "large" term infant. Nothing is known on the pregnancy. Extreme microphthalmia was observed on one side and colobomatous microphthalmia on the other. Speech and walking were delayed. Surgical treatment of bilateral cryptorchidism failed at age 10 and was followed by testosterone supplementation. Obesity appeared in infancy. The patient attended special school. At age 16, in a depressive state, he attempted suicide and was admitted to a psychiatric hospital, were he spent the rest of his life.

When seen at age 38, he was 169 cm tall, weighed 82 kg, and had an OFC of 55.5 cm. The face was not remarkable, except for mild telecanthus (39 mm) and large, beaked nose with raised bridge and downturned tip (Fig. 2a,b). He had sinistroconvex scoliosis, knock knees, flat feet, and a stiff right thumb. Obesity was of the gynaecoid type, with impressive bilateral gynaecomastia (Fig. 2c). There was marked hypogenitalism: no beard, scant axillary and pubic hair, the latter with a feminine aspect, empty scrotum, and a very short penis (35 mm, stretched) sunken in the pubic fat. Neurologic examination disclosed mild pyramidal signs and enlarged cerebral ventricles (Evans index 0.33). Ophthalmologic examination documented unilateral colobomatous microphthalmia (corneal diameter 7 mm) with nystagmus and partial cataract. The other eye was clinically absent. Karyotype was 46,XY normal. Metabolic screening and dermatoglyphics were not remarkable. Endocrinologic investigations showed mild insulin resistance compatible with prediabetes mellitus type II, low serum testosterone and dihydrotestosterone, low FSH and LH unresponsive to LHRH stimulation test, normal basal TSH, normal HGH and cortisol response to insulin stimulation test, and normal serum adrenocorticosteroids. IQ was 60.

***Family history.*** An elder brother died in infancy of congenital heart defect. Parents were nonconsanguineous, normally developed Belgians. The mother died suddenly at age 70. Parents were 29 and 34 years old, respectively, at the time of birth.

### Patient 3

This girl was born at term with a BW of 3,120 g. The pregnancy was complicated by maternal hypertension. She was markedly hypotonic during infancy with poor feeding. Right extreme microphthalmia and left microphthalmic coloboma were noted. She was globally delayed and did not walk until age 4 years. Excessive weight gain was noted from 5 years. She had normal menarche at 14 years.

On examination at 14.5 years, her head circumference was 50.3 (–3 DS), her height 142 cm (–3 SD), and her weight 83.2 kg (+5 SD) (Fig. 3a). She had a round face. Her left eye was microphthalmic with an obvious coloboma. The chorioretinal coloboma could be seen clearly through the pupil. Because of the marked nystagmus, associated retinopathy was not completely ruled out. Vision was poor. The right eye was replaced by a prosthesis. She had a high nasal bridge and a prominent bulbous nose (Fig. 3b). Her mouth, teeth, and palate were normal. Her ears were posteriorly angulated with prominent ear lobes. Her hair was thick, with a low posterior hairline. She had marked truncal obesity. There was distal joint hyperextensibility and limited extension at the elbows with a wide carrying angle. The thumbs were proximally placed. There were no psychiatric symptoms, and her food intake were not described as excessive.

Investigations included normal 46,XX karyotype, normal plasma aminoacids, normal liver and thyroid function, and normal calcium metabolism. X-rays films of pelvis and spine were normal.

***Family history.*** She had a normal brother and sister and another sister with spina bifida, who died at 6 weeks. The mother had two early miscarriages. Her British parents were healthy, with no relevant familial history.

## DISCUSSION

Bardet-Biedl syndrome (BBS) was defined in the 1920s as the combination of retinitis pigmentosa (RP) polydactyly, obesity, sexual infantilism [Bardet, 1920], and mental retardation [Biedl, 1922], recessively inherited. The clinical picture is considered much variable, with an incidence of 85–100% for tapetoretinal dystrophy of variable fundoscopic appearance, atypical RP in a few cases, 88–100% obesity, 41–87% psychic disorder (usually borderline to mild mental retardation), 45–74% hypogenitalism, and 58–85% polydactyly and/or syndactyly, as estimated in several reviews [Bell, 1958; Green et al., 1989; Klein and Ammann, 1969]. Some of those signs are age-dependent (e.g., hypogonadism in prepubertal girls, or retinal anomalies in very young children). Usually, 4 out of 5 signs are required in a patient, or collectively in a sibship to make the diagnosis, although retinal anomaly, is almost mandatory in adult cases and usually results in complete blindness by age 30. Brachydactyly is noted frequently, and urinary tract anomalies are present in 90% of cases [Green et al., 1989]. Diabetes mellitus is common in adults. Males are sterile and they appear to suffer from primary hypogonadism. Some BBS women have true hypogonadotropism. Others have high LH levels similar to what is observed in micropolycystic ovary syndrome, but in most cases, there is no identi-

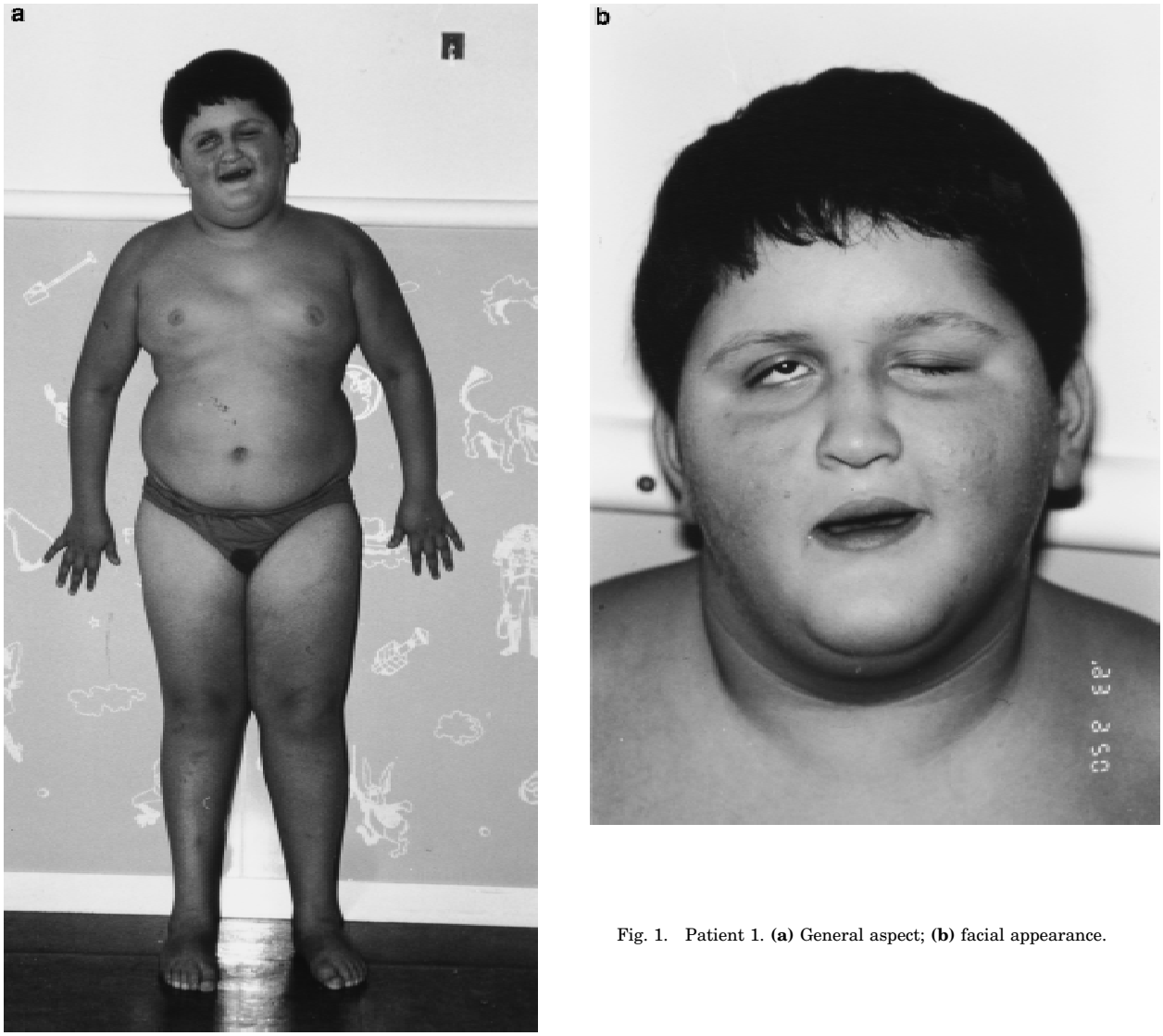


Fig. 1. Patient 1. **(a)** General aspect; **(b)** facial appearance.

fiable primary or secondary endocrinological dysfunction and only reduced fertility [Green et al., 1989]. BBS has been shown to be genetically heterogeneous (being thus a phenotype, not a syndrome), with at least four loci in 11q13 (BBS1 [Leppert et al., 1994]), 16q21 (BBS2 [Kwitek-Black et al., 1993]), 3p12 (BBS3 [Sheffield et al., 1994]), and 15q23 (BBS4 [Carmi et al., 1995]). Up to now, no clear clinical differences seem to exist between those forms. Familial studies showed an excess of obesity, hypertension, diabetes mellitus, or kidney disorder, but the major endocrinological, ophthalmologic, and skeletal features do not appear in obligate heterozygous [Croft and Swift, 1990].

Besides genetic heterogeneity of the Bardet-Biedl phenotype, clinical variations have been observed, which were considered as specific enough to allow delineation of separate entities. Laurence-Moon syndrome is the best example. The original family [Laurence and Moon, 1866; Hutchinson, 1990] consisted of three brothers and a sister with RP with onset in infancy, severe chorioretinal atrophy, short stature, low intelligence, spastic paraplegia, gynaecomasty, and cryptorchidism (in 2 males), but no polydactyly. One of the patients was reported as "fat" and two others as "heavy" in the original report, but only one patient was still obese in the follow-up. The Laurence-Moon syndrome unfortunately was lumped with BBS by Solis-Cohen and Weiss [1925]. Despite very early rejection of this lumping [Panse, 1927; Franceschetti and Klein, 1948], the use of the term "Laurence-Moon-Bardet-Biedl syndrome" still persists in common pediatric use and causes confusion.

In older reports, "Froelich adiposogenital dystrophy" encompassed BBS, Prader-Willi, and Cohen syndromes. Although Prader-Willi syndrome patients may show mild fundoscopic anomalies and Cohen syndrome cone-rod dystrophy, they do not have coloboma or polydactyly. Other less common entities combining hypogenitalism and eye anomalies, delineated as variants of BBS, include Biemond syndrome type 2, Sussman, Alström-Hallgren, and Edwards-Sethi syndromes.

Although Biemond is credited with the description of


Fig. 2. Patient 2. **a:** Frontal and **(b)** profile illustrating the prominent nose; **(c)** general aspect. Note gynaecomastia.

Fig. 3. Patient 3. General aspect.

the syndrome that held his name, the first report of a BBS-like condition with coloboma is probably by Ratner [1927]. Further cases published as BS2 syndrome include the families described by Van Bogaert and Delhaye [1936], Grebe [1953, 1960], patient 58 of Klein an Ammann [1969], and two patients of Kissel et al. [1968]. Other patients were published as BBS, with coloboma or microphthalmia considered equivalent to RP. Those include the cases of Warkany and Weaver [1940], Agnello [1948], Schachter and Ourgaud [1948], Staub and Heberling [1952], and Blumel and Knikel [1959]. Finally, cases of BBS with RP and coloboma were reported by Cavallacci [1937, 1939], and Klein and Ammann [1969, patient 43]. Several other possible cases showing a combination of polydactyly and microphthalmia or coloboma were not considered here because of insufficient data, poor description, or lack of follow-up, i.e., the children reported by Ciotola [1938] (a 1-year-old "intelligent" boy with coloboma, polydactyly and cryptorchidism, and a 1-year-old boy with coloboma and zygodactyly). Many other cases of coloboma associated with polydactyly exist in the older literature [see Ciotola, 1938; Bornstein, 1952, for references]. Most observations describe newborn or stillborn infants. They likely deal with trisomy 13 or the Meckel syndrome.

Sussman syndrome refers to the combination of short stature, infantile aspect of breasts, genitalia and uterus (with normal menses), obesity, polydactyly of feet, external ophthalmoplegia, ptosis, hypoplasia of the hypothenar areas, and microcephaly observed in a mentally retarded 19-year-old girl with normal fundi [1951].

Alström-Hallgren syndrome [Alström et al., 1959] is a recessively inherited combination of atypical RP (characterised by early loss of central vision), deafness, obesity, and diabetes mellitus (with insulin resistance and acanthosis nigricans), distinguished from BBS by the absence of hypogonadism and mental retardation. Sensory defects are similar to those seen in Usher syndromes. Chronic nephropathy and cardiomyopathy are associated anomalies.

Edwards-Sethi syndrome [Edwards et al., 1976; Boor et al., 1993] is an autosomal recessive condition closely related (and possibly allelic) to Alström-Hallgren syndrome, comprizing RP, deafness with labyrinthine involvement, mental retardation, cerebral and cerebellar atrophy, hypogonadism, diabetes mellitus with acanthosis nigricans, and short stature.

## REVISED NOSOLOGY OF CASES WITH BIEMOND SYNDROME TYPE 2

A review of the reports dealing with BBS phenotype with coloboma yielded an extraordinarily heterogeneous material, whatever initial diagnosis suggested by the authors. We suggest a new nosology for those cases and have sorted them into six clinical phenotypes, three being "new" entities.

### Bardet-Biedl Syndrome

Obviously, there is no reason to exclude BBS because of the presence of a coloboma, if retinal dystrophy coexists with coloboma. Such cases are uncommon: 1/212 in the review by Schachat and Maumenee [1982] of BBS syndromes published between 1959 and 1982. No instance was reported in sibs; thus coincidental syndromy is not excluded. Cavallacci [1939] described a "complete" case of BBS (with RP) and bilateral iris coloboma. Prosperi and Ciuffi [1969, case 1] described a case of BBS with unilateral coloboma, ectopia lentis and ptosis, born to consanguineous parents. Klein and Ammann [1969] reported on a 6-year-old girl with atypical RP, obesity, polydactyly, microcephaly, mental retardation, and parapapillar choroidal coloboma (case 43). Finally, Staub and Heberling [1952] reported on a family in which three sibs had typical BBS syndrome, RP, and correctopia. It should be remembered that in some instances of retinal dystrophy, macular pseudocoloboma (i.e., aplasia) may be observed and erroneously considered as "true" coloboma.

### Biemond Syndrome Type 2, sensu stricto

The original family [Biemond, 1934] consisted of two sibs born to alcoholic Dutch first cousins. The sibship

included 14 children, 7 of whom died in infancy of ill-defined neurologic disorder(s). The propositus was a 19-year-old, 148-cm-tall man with sexual infantilism, atrophic/cryptorchid testes, and unilateral coloboma. His sister had hypogonadism and duplicated right thumb ("een dubbelen duim"). She died suddenly. Necropsy showed syringomyely, hydrocephalus, brain tumour (glioma ?), and diffuse polyposis coli. Both had a very small sella turcica. They were described as childish but not mentally retarded. Obesity was not a trait in this family. Psychologic disturbance may be unrelated to the syndrome, considering the alcoholism of their parents. Brain tumour and polyposis coli, observed in the original female case, likely represent fortuitous coexistence of Turcot syndrome, or freshly mutated APC. Thus, BS2 may be defined as a combination of hypogonadism, short stature, inconstant preaxial polydactyly and coloboma, recessively inherited. None of the subsequently reported cases resemble closely this original report, and none of them was ever described with preaxial polydactyly.

### Coloboma-Obesity-Hypogenitalism-Mental Retardation Syndrome

Cavallacci [1937] reported on a mother with bilateral noncolobomatous microphthalmia, unilateral cataract, atypical RP, obesity, and borderline intelligence. She had five children, including one early deceased with microphthalmia, and a girl with severe microphthalmia and cataract (fundus not examinable), obesity (from infancy to age 15), hypogonadism, and mental retardation. François [1953] described a family in which apparently pure microphthalmia segregated for four generations with low penetrance. One of the affected patients, married with an unaffected cousin, had one child with isolated microphthalmia, and another with bilateral anophthalmia, mental retardation, and "adiposogenital" syndrome, (no details). The author hypothesized that this girl could be homozygous for a coloboma gene. A further case was reported by Grebe [1953, 1960]; the propositus had bilateral colobomatous microphthalmia with "partial aniridia," obesity, borderline retardation, but no polydactyly. Three close relatives (her great-grandfather, her cousin, and the child of the latter), and more than 20 distant relative had nonsyndromal coloboma, transmitted as an irregularly dominant trait. Besides coloboma, a distantly related affected women (patient IV-41) had epilepsy and an arachnoid cyst. Other relatives had epilepsy or hip luxation, which were probably fortuitous. These three families are thus characterised by autosomal dominant inheritance of colobomatous microphthalmia. A few patients develop obesity, hypogonadism, and mental retardation. Polydactyly was not observed. In Cavallacci's case, RP was present but atypical. In the latter report, the mother had partial expression of the syndrome, in contrast to the Grebe and François families, in which patients do not exhibit an intermediate phenotype.

Ratner [1927] described a woman with obesity, mental retardation, iridochoroidal coloboma, and epilepsy. Van Bogaert and Delhaye [1936] reported a boy with coloboma, mental retardation, hypogenitalism, and obesity. The two latter signs were present in one of his cousins and one maternal aunt, whereas his mother, the mother of his cousin, and his grandparents appeared unaffected. The child described by Warkany and Weaver [1940] as atypical BBS had truncal obesity, unilateral microphthalmia with cloudy cornea, hypogenitalism with cryptorchidism, microcephaly, and mental retardation. Agnello [1948] reported as BBS ("Froelich syndrome") a woman with obesity, hypogenitalism, mental retardation, enlarged parietal foramina, choroidal coloboma on one side, and microphthalmia with cataract on the other side. Patient 2 in Kissel et al. [1968] was a girl with short stature, obesity, hypogonadism, coloboma with unilateral cataract, platybasia with occipito-atlantoid synostosis, and transmission deafness. Patient 3 by Hecker and Warren [1937] had coloboma, hypogenitalism with cryptochidism, obesity, stubby fingers, and mental retardation.

We suggest that all of the above reports may deal with a previously undelineated syndrome also present in our three patients. Major features are mental impairment, coloboma, and obesity. Hypogenitalism is less constant. As in BBS, women with the syndrome may be fertile. Our patient three menstruated normally. The delineation of this syndrome is based on phenotype only. Only Cavallaci family members show clear autosomal dominant inheritance, whereas other cases are sporadic (without parental consanguinity), or appear in families with purely ocular problem. Whereas variable expression of a dominant mutation is the simpler explanation for the coexistence of "partial" (pure coloboma) and full forms in familial cases, coexistence of BBS and common microphthalmia, heterogeneity, or other nonallelic interference have to be considered. Of special interest are the observation of the nonrandom association of microphthalmia and hypothalamic dysfunction. Bierich et al. [1991] observed partial hypothalamic hypopituitarism in three patients with isolated colobomatous microphthalmia or anophthalmia, without mental retardation. They suggested that hypothalamic hypopituitarism may be a component of any syndrome with severe microphthalmia and parallel this association with septo-optical dysplasia, which is almost invariably associated with organic hypopituitarism (and exceptionally, with microphthalmia) [Kemmann and Jones, 1977]. Simultaneously, Keppen et al. [1990] showed hypogonadotropic hypogonadism in a group of five patients with severe microphthalmia or anophthalmia and variable mental retardation. The five patients were clinically heterogeneous. The pathogeny could be a midline developmental field defect affecting the area that would ultimately develop into eyes and hypothalamus.

Further complexity in the nosology comes from a report [Al Frayh and Haque, 1987] on a combination of IUGR, microcephaly, anophthalmia/severe colobomatous microphthalmia, cleft palate, small penis with cryptorchidism, heart defect, hypotonia, and overriding fingers and toes or arthrogryposis, observed in two sibs born to consanguineous parents. Microcephaly, growth retardation, absence of obesity, and severe mental im-

pairment are distinctive traits of this syndrome (which is possibly related to the CHARGE association), but the clinical overlap with the syndrome discussed here implies that genetic counselling in isolated cases should be cautious.

In a case by Schachter and Ourgaud [1948], aniridia, mental retardation, short stature, and hypogonadism where associated. Aniridia combined with zonular cataract and polydactyly was discussed as partial form of BBS by Bornstein [1952] in a child born of consanguineous parents. Those reports remain unclassifiable, although chromosomal anomaly (as WAGR, or 22q11 deletions) are not excluded in either. Shenkman [1987] described a nonretarded 46-year-old man with coloboma and adult onset hypogonadism, who was considered as BS2 in POSSUM, an opinion with which we disagree.

### "New" Lethal MCA Syndrome With Coloboma, Hypospadias, and CNS Malformations

In a review of BBS [Blumel and Kniker, 1959], three sibs were described who died in infancy. All of them had hydrocephalus and epilepsy. Unilateral iris coloboma, hydronephrosis, VSD, pulmonary stenosis, micropolygyria, and agenesis of the corpus callosum were shown in one. Each of them has postaxial polydactyly of feet and severe hypospadias, without cryptorchidism. Hypertelorism can be suspected on the illustration. Their father, his sister, and a great-grandfather had postaxial polydactyly of feet. This anomaly could either be fortuitous or represent partial expression of the disorder (which would then be dominantly inherited). Obesity was not a manifestation, and retinal anomalies were not mentioned.

This family is quoted several times as example of BS2 (e.g., in LDDB and OMIM); however, we think this pedigree must be set apart from BBS and BS2. Unbalanced chromosome translocation could result in such a phenotype. The recessively inherited acrocallosal, hydrolethalus and severe Smith-Lemli-Opitz syndromes partially overlap with this family. Opitz GBBB and coloboma-hypospadias syndromes [Halal and Farsky, 1981] are dominantly transmitted, but do not show polydactyly. Pallister-Hall syndrome could be considered, as it is dominantly inherited, and polydactyly may be the only expression in mildly affected cases, but oral or laryngeal anomalies and brachydactyly are not mentioned. Buntinx and Majewski [1990] described a single male infant with coloboma, agenesis of the corpus callosum, hydronephrosis, abnormal ears with deafness, and polydactyly. This patient shared many points with Blumel's family, although hypospadias was not present in their case. Considering the available data, no definite diagnosis can be reached in this family, and we suggest to keep it as a special "private" entity.

### Coloboma-Zygodactyly-Clefting Syndrome

Two patients labelled Biemond syndrome type II were reported by Kissel et al. [1968]. Patient one was a boy with hypertelorism, wide, downslanting palpebral fissures (apparently with everted lower lid), right external ophthalmoplegia, iridoretinal and lens coloboma, dermoid cyst of the right upper lid, short stature, and severe mental retardation. Bilateral labiopalatine cleft, zygodactyly, ankylosis of knees, cryptorchidism, hypospadias, and hypoplastic tragi were also present. Facially there are similarities with Kabuki syndrome, but zygodactyly and ankylosis of the knee are unexpected. Ear dysplasia, coloboma, and knee ankylosis may be seen in the Bard [1979] type of contractural arachnodactyly, but there is no mention of a Marfanoid habitus. Karyotype is not available in those cases, so that mosaic triploid state is not completely ruled out. Patient 2 of Ciotola [1938] may have had the same disorder.

### Rubinstein-Taybi Syndrome

In their monograph on BBS, Klein an Ammann [1969] described as BS2 a 30-year-old woman (patient 58) with bilateral iridochoroidal coloboma, microphakia with bilateral cataract and high myopia, dwarfism (133 cm), "Crouzonoid" face (exophthalmia, hypertelorism, downslanted palpebral fissures, beaked nose, prognathism), brachydactyly with brachymetacarpalia IV and V, "slight adiposogenital dystrophy," and pronounced mental retardation. Later, Klein et al. [1972], prompted by a letter of Rubinstein, re-evaluated their case and concluded that she had Rubinstein-Taybi syndrome. This letter, written in French, was missed in successive reviews of BS2, explaining why the term "cranial dysostosis" recurrently appears in the description of the syndrome. The patient was recently re-examined by one of us. The diagnosis was confirmed by the demonstration of the Rubinstein-Taybi critical region deletion by FISH analysis.

## CONCLUSIONS

Critical review of the literature on BBS-like syndromes with coloboma yielded a large series of patients with heterogeneous manifestations, often referred to as Biemond syndrome type 2. Careful analysis of the original reports allow us to propose a classification of those observations into six clinical entities, three of them being probable "new syndromes." A large proportion of those cases seems to belong to families where most cases have a dominantly inherited colobomatous microphthalmia, whereas some of them show a severe BBS-like phenotype. Further work will be necessary to solve the pathogenesis of this condition. BS2, in our narrower sense, remains a private condition.

This analysis of the literature demonstrates clearly the need not to rely exclusively on databases or textbooks for the diagnosis of rare syndromes. It is extraordinary that the preaxial polydactyly of BS2, clearly stated in the original report, was completely overlooked in further reviews. In the *Birth Defect Encyclopedia* [Buyse, 1990], Temtamy's monograph [1978], and even MIM (210350); postaxial polydactyly is mentioned as major diagnostic criterion, and thumb duplication is not coded in LDDB [Baraitser et al., 1995] nor POSSUM [Bankier et al. 1995]. More disappointing is the complete neglect of the correction by Klein of his initial diagnosis. If a moral had to be drawn from this

work, we would suggest: "keep critical sense; use textbooks and databases, but *always* go back to the original description."

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